Claims

1. A method for synthesising a templated molecule comprising a plurality of functional groups, said method comprising the steps of

i) providing at least one template comprising a sequence of n coding elements selected from the group consisting of first coding elements and second coding elements,

wherein each coding element comprises at least one recognition group capable of recognising a predetermined complementing element, and

wherein n is an integer of at least 3,

with the proviso that the template comprises at least 3 first coding elements,

ii) providing a plurality of building blocks selected from the group consisting of first building blocks and second building blocks, with the proviso that at least 3 first building blocks are provided,

wherein each first building block comprises

a) at least one complementing entity comprising a first complementing element comprising at least one recognition group capable of recognising a predetermined first coding element,

b) at least one functional entity comprising at least one functional group and at least one functional entity reactive group, and

c) at least one spacer comprising at least one spacer reactive group, wherein the spacer is separating the at least one functional entity from the at least one complementing entity, and

wherein each second building block comprises

a) at least one complementing entity comprising a second complementing element comprising at least one recognition group capable of recognising a predetermined second coding element,

b) and at least one spacer comprising at least one spacer reactive group,

iii) complementing coding elements by contacting each coding element with a building block complementing element capable of recognising said coding element, wherein at least 2 coding elements are interacting with complementing elements simultaneously,

with the proviso that a total of at least 3 first coding elements are complemented; and

iv) forming a spacer backbone by linking neighbouring spacers in a ribosome catalysed reaction by means of reacting spacer reactive groups, and

v) obtaining a templated molecule comprising at least 3 covalently linked, functional groups by linking, by means of reacting functional entity reactive groups, a functional group of one functional entity to a functional group of another adjacently positioned, functional entity and linking said other functional entity to yet another adjacently positioned functional entity.

2. The method according to claim 1, wherein step iii) to iv) comprises the steps of

a) complementing 2 neigbouring coding elements simultaneously by contacting each coding element with a building block complementing element capable of recognising said coding element,

b) forming a spacer backbone by linking, by means of a reaction involving spacer reactive groups, the 2 building block spacers,

c) complementing at least one further predetermined coding element by contacting said coding element with a building block complementing element capable of recognising said coding element, and

d) elongating the spacer backbone by linking to the spacer backbone, by means of a reaction involving spacer reactive groups, the neighbouring building block spacer.

3. The method according to claim 2, wherein the steps of the method are performed in the order mentioned.

4. Method of claim 2, wherein steps c) and d) are repeated at least twice, such as repeated at least three times, for example at least 4 times, such as at least 5 times, for example at least 10 times, for example at least 15 times, such as at least 20 times, for example at least 30 times, such as at least 40, for example at least 50, such as at least 75 times, for example at least 100 times, such as at least 150 times, for example at least 200 times.

5. Method of claim 2, wherein steps c) and d) are repeated between 2 and preferably 10,000 times, for example between 5 and preferably 1000 times, such as between 10 and preferably 500 times.

6. The method according to any of claims 1 to 5, which furthermore comprises the step of

iva) breaking the covalent bond between the spacer backbone and at least one complementing element.

7. The method according to claim 6, wherein the step iva) is performed once after every performance of step iv) of claim 1 or once after every performance of step b) or d) of claim 2.

8. The method according to any of claims 1 to 7, which furthermore comprises the step of

v) breaking the covalent bond between the spacer backbone and at least one functional entity.

9. The method according to claim 8, wherein the covalent bond is selected from the group consisting of cleavable linkers and selectively cleavable linkers.

10. The method according to claim 8, wherein all covalent bonds between the spacer backbone and the functional entities are broken except for one.

11. The method according to any of claims 1 to 10, wherein the template comprises a ratio of first coding elements to second coding elements of 50:1, such as 40:1, for example 30:1, such as 25:1, for example 20:1, such as 15:1, for example 10:1, such as 8:1, for example 6:1, such as 5:1, for example 4:1, such as 3:1, for example 2:1, such as 1:1, for example 1:2, such as 1:3, for example 1:4, such as 1:5, for example 1:6, for example 1:7, such as 1:8, for example 1:10, such as 1:15, for example 1:20, such as 1:25, for example 1:30, such as 1:40, for example 1:50.

12. The method according to any of claims 1 to 11, wherein the template comprises at least 1, for example at least 2, such as at least 3, for example at least 4, such as at least 5, for example at least 10, for example at least 15, such as at least 20, for example at least 30, such as at least 40, for example at least 50, such as at least 75, for example at least 100, such as at least 150, for example at least 200 elements first coding elements.

13. The method according to any of claims 1 to 12, wherein the template comprises at least 1 for example at least 2, such as at least 3, for example at least 4, such as at least 5, for example at least 10, for example at least 15, such as at least 20, for example at least 30, such as at least 40, for example at least 50, such as at least 75, for example at least 100, such as at least 150, for example at least 200 second coding elements.

14. The method according to any of claims 1 to 13, wherein the ribosome is a wild type ribosome.

15. The method according to any of claims 1 to 14, wherein the spacer backbone only comprises spacer residues that are directly attached to a functional entity.

16. The method according to any of claims 1 to 15, wherein the spacer backbone comprises spacer residues that are directly attached to a functional entity, wherein every two spacer residues that are directly attached to a functional entity are separated by a minimum of 0 spacer residues that are not directly attached to a functional entity, for example at least 1, such as at least 2 first, for example around 2, such as around 3, for example around 4, such as around 5, for example around 6, for example around 7, such as around 8 to 10, for example around 10 to 15, such as around 15 to 20, for example around 20 to 30 spacer residues, that are not directly attached to a functional entity.

17. The method according to any of claims 1 to 16, wherein the spacer backbone has the form of an α-helix.

18. The method according to any of claims 1 to 17, wherein the spacer backbone has the form of a coiled coil.

19. The method according to any of claims 1 to 18, wherein the spacer backbone has a form selected from the group consisting of β-sheets, beta-turn, beta-helix, helix-turn helix, part of a collagen structure, or part of a zinc finger structure.

20. The method according to any of claims 1 to 19, wherein the spacer backbone is denatured and bound to a solid surface that determines the shape of the spacer backbone.

21. The method according to claim 17, wherein the spacer backbone comprises one functional entity per helical turn of the spacer backbone.

22. The method according to claim 17, wherein the spacer backbone comprises a functional entity for every 4 spacer residues.

23. The method according to any of claims 1 to 22, wherein n is an integer of more than 1 and less than 1000, for example between 5 and 500, such as between 10 and 100.

24. The method of any of claims 1 to 23, wherein the spacer backbone is a linear sequence of spacers.

25. The method according to any of claims 1 to 24, wherein the complementing entity is a tRNA like structure.

26. The method according to any of claims 1 to 25, wherein the complementing entity is a tRNA.

27. The method according to any of claims 1 to 26, wherein the complementing entity is a pseudoknot.

28. The method of any of claims 1 to 27, wherein the complementing elements are selected from the group consisting of nucleotides, nucleotide derivatives, nucleotide analogues, and any combination thereof.

29. The method according to any of claims 1 to28, wherein each complementing element consists of 1 nucleotide, such as 2, for example 3, such as 4, for example 5, such as 5 to 10, for example 10 to 15, such as 15 to 20, for example more than 20.

30. The method of claims 28 or 29, wherein the nucleotides are ribonucleic acids comprising a base selected from adenine (A), uracil (U), guanine (G), and cytosine (C) and derivatives and analogues thereof.

31. Method according to any of claims 1 to 30, wherein the complementing element is an anticodon.

32. Method according to any of claims 1 to 30, wherein the template is nucleic acid.

33. Method according to any of claims 1 to 32, wherein the template is a nucleic acid, which can be template of a ribosome mediated translation.

34. Method according to claim 33, wherein the template comprises or consists of RNA or a derivative or analogue thereof.

35. The method according to any of claims 32 to 34, wherein the template comprises RNA residues that are modified on the 2' position of the ribose moiety.

36. The method according to any of claims 1 to 35, wherein the template is capped RNA.

37. The method according to any of claim 1, wherein the template is mRNA.

38. The method according to any of claims 1 to 37, wherein the template is tethered to puromycin.

39. The method of any of claims 1 to 38, wherein the coding elements are selected from the group consisting of nucleotides, nucleotide derivatives, nucleotide analogs, and any combination thereof.

40. The method according to any of claims 1 to 39, wherein each coding element consists of 1 nucleotide, such as 2, for example 3, such as 4, for example 5, such as 5 to 10, for example 10 to 15, such as 15 to 20, for example more than 20.

41. The method of claim 40, wherein the nucleotides are ribonucleic acids comprising a base selected from adenine (A), uracil (U), guanine (G), and cytosine (C) and derivates and analogues thereof.

42. Method according to any of claims 1 to 41, wherein the coding element is a codon.

43. The method according to any of claims 1 to 42, wherein the spacer is selected from the group consisting of amino acids.

44. The method according to any of claims 1 to 43, wherein the spacer is selected from the group consisting of α-amino acids.

45. Method according to claim 43, wherein the amino acid is a standard amino acid residue or a derivative thereof.

46. The method according to any of claims 1 to 45, wherein the spacer consists of a naturally occurring amino acid residues including the entire side-chain and wherein the spacer does not form part of the functional entity.

47. Method according to claim 43, wherein the amino acid is a non-standard amino acid.

48. Method according to claim 43, wherein the amino acid is a modified standard amino acid.

49. The method according to any of claims 1 to 48, wherein each spacer comprises at least 1, such as 2, for example 3, such as more than 3 spacer reactive groups.

50. Method according to any of claims 1 to 49, wherein the spacer reactive groups are selected from the group consisting of acyls and amines.

51. The method according to any of claims 1 to 50, wherein each spacer comprises one spacer reactive group, which is an acyl and another spacer reactive group which is an amine.

52. Method according to any of claims 1 to 3, wherein linking according to step iv) consists of the formation of an amide-bond.

53. The method according to any of claims 1 to 3, wherein the adjacently positioned functional entities are positioned sequentially on the spacer backbone.

54. The method of any of claims 1 to 3, wherein the functional entities are selected from the group consisting of α-amino acids, β-amino acids, γ-amino acids, ω-amino acids.

55. The method of any of claims 1 to 3, wherein the templated molecule comprises or essentially consists of amino acids selected from the group consisting of α-amino acids, β-amino acids, γ-amino acids, ω-amino acids.

56. The method of any of claims 1 to 3, wherein the templated molecule comprises or essentially consists of α-amino acids.

57. The method of any of claims 1 to 3, wherein the templated molecule comprises or essentially consists of monosubstituted α-amino acids.

58. The method of any of claims 1 to 3, wherein the templated molecule comprises or essentially consists of disubstituted α-amino acids.

59. The method of any of claims 1 to 3, wherein the templated molecule comprises or essentially consists of monosubstituted β-amino acids.

60. The method of any of claims 1 to 3, wherein the templated molecule comprises or essentially consists of disubstituted β-amino acids.

61. The method of any of claims 1 to 3, wherein the templated molecule comprises or essentially consists of trisubstituted β-amino acids.

62. The method of any of claims 1 to 3, wherein the templated molecule comprises or essentially consists of tetrasubstituted β-amino acids.

63. The method of any of claims 59 to 62, wherein the backbone structure of said β-amino acids comprises or essentially consists of a cyclohexane-backbone and/or a cyclopentane-backbone.

64. The method of any of claims 1 to 3, wherein the templated molecule comprises or essentially consists of γ-amino acids.

65. The method of any of claims 1 to 3, wherein the templated molecule comprises or essentially consists of ω-amino acids.

66. The method of any of claims 1 to 3, wherein the templated molecule comprises or essentially consists of vinylogous amino acids.

67. The method of any of claims 1 to 3, wherein the templated molecule comprises or essentially consists of N-substituted glycines.

68. The method of any of claims 1 to 3, wherein the templated molecule comprises or essentially consists of funtional groups and/or functional entities selected from the group of α-peptides, β-peptides, γ-peptides, ω-peptides, mono-, di- and tri-substituted α-peptides, β-peptides, γ-peptides, ω-peptides, peptides wherein the amino acid residues are in the L-form or in the D-form, vinylogous polypeptides, glycopoly-peptides, polyamides, vinylogous sulfonamide peptide, polysulfonamide, conjugated peptides comprising e.g. prosthetic groups, polyesters, polysaccharides, polycarbamates, polycarbonates, polyureas, polypeptidylphosphonates, polyurethanes, azatides, oligo N-substituted glycines, polyethers, ethoxyformacetal oligomers, poly-thioethers, polyethylene glycols (PEG), polyethylenes, polydisulfides, polyarylene sulfides, polynucleotides, PNAs, LNAs, morpholinos, oligo pyrrolinone, polyoximes, polyimines, polyethyleneimines, polyimides, polyacetals, polyacetates, polystyrenes, polyvinyl, lipids, phospholipids, glycolipids, polycyclic compounds comprising e.g. aliphatic or aromatic cycles, including polyheterocyclic compounds, proteoglycans, and polysiloxanes, inlcuding any combination thereof.

69. The method of any of claims 1 to 3, wherein neighbouring residues of the templated molecule is linked by a chemical bond selected from the group of chemical bonds consisting of peptide bonds, sulfonamide bonds, ester bonds, saccharide bonds, carbamate bonds, carbonate bonds, urea bonds, phosphonate bonds,urethane bonds, azatide bonds, peptoid bonds, ether bonds, ethoxy bonds, thioether bonds, single carbon bonds, double carbon

bonds, triple carbon bonds, disulfide bonds, sulfide bonds, phosphodiester bonds, oxime bonds, imine bonds, imide bonds, including any combination thereof.

70. The method of any of claims 1 to 3, wherein the backbone structure of said templated molecule comprises or essentially consists of a molecular group selected from -NHN(R)CO- ; -NHB(R)CO- ; -NHC(RR')CO- ; -NHC(=CHR)CO- ; $-NHC_6H_4$ CO-; $-NHCH_2$ CHRCO-; $-NHCHRCH_2$ CO- ; $-COCH_2$- ; -COS- ; -CONR- ; -COO- ; -CSNH- ; $-CH_2$ NH- ; $-CH_2CH_2$- ; $-CH_2$ S- ; $-CH_2$ SO- ; $-CH_2SO_2$- ; $-CH(CH_3)$S- ; -CH=CH- ; -NHCO- ; -NHCONH- ; -CONHO- ; -C($=CH_2$)CH_2- ; $-PO_2^-NH$- ; $-PO_2^-CH_2$- ; $-PO_2^-CH_2N^+$- ; $-SO_2NH^-$- ; and lactams.

71. The method of any of claims 1 to 3, wherein the templated molecule comprises or essentially consists of at least 2 different functional groups, such as at least 3 different functional groups, for example at least 4 different functional groups, such as at least 5 different functional groups, for example at least 6 different functional groups, such as at least 7 different functional groups, for example at least 8 different functional groups, such as at least 9 different functional groups, for example at least 10 different functional groups, such as more than 10 different functional groups.

72. The method of any of claims 1 to 3, wherein the functional groups are identical.

73. The method according to any of claims 1 to 3, wherein each functional entity comprises more than one, such as 2, for example 3, such as 4, for example 5, such as more than 5 functional entity reactive groups.

74. The method according to any of claims 1 to 3, wherein the functional entity reactive groups are selected from the group consisting of N-carboxyanhydride (NCA), N-thiocarboxyanhydride (NTA), amine, carboxylic acid, ketone, aldehyde, hydroxyl, thiol, ester, thioester, any conjugated system of double bonds, hydrazine, N-hydroxysuccinimide ester, and epoxide.

75. The method according to claim 74, wherein the functional entity reactive group is an electrophile.

76. The method according to claim 75, wherein the functional entity reactive group is a nucleophile.

77. The method according to claim 76, wherein the functional entity reactive group is a radical.

78. A template/templated molecule complex comprising a template and a templated molecule, wherein the template encodes the synthesis of the templated molecule and wherein said templated molecule comprises at least 3 covalently linked functional groups.

79. A template/templated molecule complex comprising a template and a templated molecule, wherein the template templates the synthesis of the templated molecule and wherein said templated molecule comprises at least 3 covalently linked functional groups, with the proviso, that the templated molecule is not a standard polypeptide.

80. The complex according to any of claims 78 and 79, wherein the complex furthermore comprises a spacer backbone.

81. The complex according to claim 80, wherein the spacer backbone is linked to the templated molecule by 1, such as 2, for example 3, such as more than 3 covalent bonds.

82. The complex according to any of claims 78 and 79, wherein the template is linked to the templated molecule via a puromycin linker.

83. A plurality of templated molecules, wherein the plurality comprises at least 1000 different templated molecules and wherein said templated molecule comprises a sequence of at least 3 functional groups, each encoded by a coding element of a template, with the proviso, that the templated molecule is not a standard polypeptide.

84. A plurality of template/templated molecule complexes comprising at least 1000 different template/templated molecule complexe, wherein each template/templated molecule complex is a complex according to any of claims 78 and 79.